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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,074	09/25/2006	Haruhisa Ogita	0020-5517PUS1	1823

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
07/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,074	OGITA ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/25/2006;12/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

Two Foreign references were struck as copies were not provided. Only a single sheet for each was provided.

Election/Restrictions

Applicant's election with traverse of Group I, a method for regulating the immune system and treatment of allergies; in the reply filed on 05/04/2009 is acknowledged. The traversal is on the ground(s) that this should have been done as an election of species. This is not found persuasive because e.g. treating HIV infection and treating autoimmune disorders are clearly distinct inventions, and not species of one invention, and applicants have presented no specific argument (or evidence) to the contrary. As it happens, the claim is not allowable, so the distinction is (presently) moot anyway.

The requirement is still deemed proper and is therefore made FINAL.

Claim 19 is rejected as being drawn to an improper Markush Group. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. This does not constitute an art recognized genus, and the claims are deemed to lack unity of invention (see ***In re Harnish***, 206 USPQ 300). The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter will overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-21 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 2004029054.

The reference can best be viewed as US 20060052403. The reference has numerous species falling within these claims, corresponding to R1 as alkyl or alkoxy-alkyl, X1 as a O, S or NH, Z as methylene or ethylene. Utility is the same. The rejection might be overcome by submission of certified translation of priority documents. Claim 20 is seen in the last steps of process #1.

The examiner notes in this regard US 20060052403 itself, but the reference has no 102(e) date.

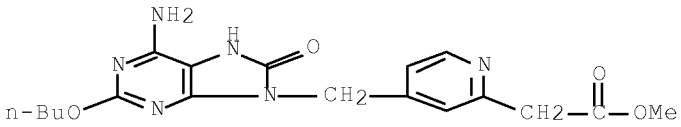
Claim Rejections - 35 USC § 103

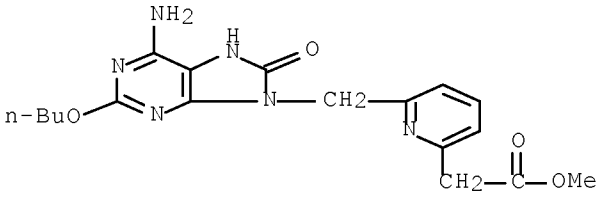
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

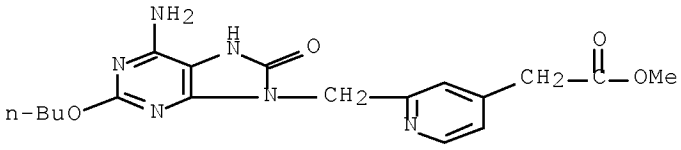
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

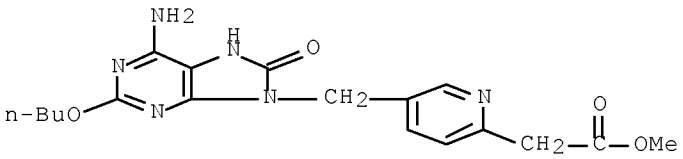
Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over by WO 2004029054.

Although there do not appear to be any species in common between the two documents, the differences are quire small. For example, the claim has these three species:







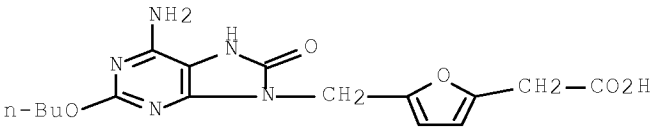
Whereas the reference has  .

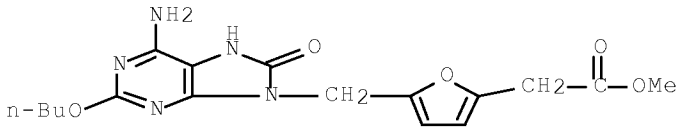
The reference species is just a position isomer of all three of the above species. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: ***Ex parte Englehardt***, 208 USPQ 343, 349; ***In re Mehta***, 146 USPQ 284, 287; ***In re Surrey***, 138 USPQ 67; ***Ex Parte Ullyot***, 103 USPQ 185; ***In re Norris***, 84 USPQ 459; ***Ex***

Parte Naito, 168 USPQ 437, 439; ***Ex parte Allais***, 152 USPQ 66; ***In re Wilder***, 166 USPQ 545, 548; ***Ex parte Henkel***, 130 USPQ 474; ***Ex parte Biel***, 124 USPQ 109; ***In re Petrzilka***, 165 USPQ 327; ***In re Crownse***, 150 USPQ 554; ***In re Fouche***, 169 USPQ 431; ***Ex parte Ruddy***, 121 USPQ 427; ***In re Wiechert***, 152 USPQ 247, ***In re Shetty***, 195 USPQ 753; ***In re Jones***, 74 USPQ 152, 154; and ***In re Mayne***, 41 USPQ2d 1451 (in which the Court took notice of the extreme similarity between the amino acids Leucine and isoleucine: "In fact, Leu is an isomer of Ile -- an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains...of Leu and Ile have the same number of hydrogen and carbon atoms...The structure of Leu and Ile alone suggest their functional equivalency" (at 1454-1455)).

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (Englehardt) and "Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original). Note also ***In re Jones***, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to prima facie obviousness"; one of those listed is "adjacent homologues and structural isomers". Position isomers are the basic form of close "structural isomers." Similar is ***In re Schechter and LaForge***, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also ***In re Deuel*** 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds ... a known compound may suggest its

analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para)." See also MPEP 2144.09, second paragraph.

Similarly, the claim has 

The reference has  .

These differ in that one is the acid, and one is the methyl ester. However, the reference teaches the equivalence of the two, and has examples of both acids and methyl esters.

Other examples could be given.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., ***In re Berg***, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); ***In re Goodman***, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); ***In re Longi***, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); ***In re Van Ornum***, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); ***In re Vogel***, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and ***In re Thorington***, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be

commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 89-108 and 110-132 of copending Application No. 10528343. Although the conflicting claims are not identical, they are not patentably distinct from each other because there does not appear to be a line of demarcation between the claims of the 2 cases when in 10528343, m=1. The definitions of X1 and Z are the same in both cases. The furan, thiophene and pyridine choices for A seen in this case are specifically named in e.g. claim 101 of 10528343. Note that the side chain (on the A ring) choice of COOR2 attached to alkyl is seen in e.g. claim 102 where Q2 is COOR2. The R1 choices of H, optionally substituted alkyl, and halo are all provided for in the definition of Q1-Y1 in 10528343. For example, the species 9-(3-carboxymethylbenzyl)-2-(2-ethoxyethoxy)-8-hydroxyadenine of 10594074 falls within the claims of 10528343 for m=1, Y2=methylene, and Q1=alkoxy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The C_{2-10} acyloxy group in claim 2 is unclear. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R? In carboxylic acid acyls, does the carbon count include the carbon of the carbonyl?
2. The term "acycloalkyl" (in the claim 2 list of substituents on amino) is unclear. Is this acyl-alkyl? Cycloalkyl? For whichever choice is selected, applicants must show that one skilled in the art could have figured out that this choice, and not another, was surely intended.
3. A proper composition claim must have a carrier of some kind; otherwise it is identical with a compound claim. Adding a carrier to claims 11-14 will resolve the matter.
4. The term "cyclic amino" (in R, X2, etc.) is ambiguous It could mean a) amino itself is part of a cycle, e.g. piperidinyl, b) amino is attached via a cycle, e.g. aminomethylphenyl c) a cycle is attached directly to the amino, e.g. anilino d) a cycle is attached to the amino, but not necessarily directly e.g. benzylamino or e) the term is intended to encompass two or more of these options. For whichever choice is selected, applicants must show that one skilled in the art could have figured out that this choice, and not another, was surely intended.

Claims 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-17 provide for the use of the compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Although claims 16-17 are apparently intended as a process for preparing a composition, it is impossible to tell what claim 15 intends, and the claim is not otherwise examined.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15-17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example ***Ex parte Dunki***, 153 USPQ 678 (Bd.App. 1967) and ***Clinical Products, Ltd.*** v. ***Brenner***, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to ***In re Wands***, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see ***In re Vaeck***, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the broad scope of R1 and A, trillions of compounds are covered.

(b) Scope of the diseases covered.

A. Modulating immune response is embracive of treating autoimmune disorders. The "autoimmune diseases" are processes that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes, often unknown.

There is a loosely connected group of "lupus" diseases. These include 1. Cutaneous Lupus: This includes a wide assortment of forms Acute cutaneous lupus erythematosus (ACLE), Subacute cutaneous lupus erythematosus (SCLE) are the two acute forms. Chronic cutaneous lupus erythematosus (CCLE) includes Discoid lupus erythematosus (DLE),

which also has Hypertrophic/verrucous variant and a Teleangiectoid variant and the palmar-plantar form of DLE. Other chronic forms are Lupus erythematosus profundus (LEP) and Chilblain lupus erythematosus (CHLE aka "Hutchinson lupus"). In addition, there is Intermittent cutaneous lupus erythematosus (ICLE) as well as Lupus erythematosus tumidus (LET), which is now considered a separate entity. Finally, there is the category of Bullous lesions in lupus erythematosus (BLE); 2. Systemic lupus erythematosus (SLE) which can affect any system or organ in the body including the joints, skin, lungs, heart, blood, kidney, or nervous system; 3. Drug-induced lupus erythematosus (DILE), a side effect of long-term use of certain medications; 4. Neonatal lupus, a condition acquired from the passage of maternal autoantibodies (anti-Ro/SSA or anti-La/SSB) which can affect the skin, heart and blood of the fetus and newborn; and 5. "Lupus in Overlap", in which a form of lupus overlaps with rheumatoid arthritis, Myositis, Sjogren's Syndrome, Mixed Connective Tissue Disease (generally polymyositis-dermatomyositis plus Scleroderma), or Scleroderma. These are now considered specific syndromes, not merely a case of a person happening to have two disorders.

There is a group of autoimmune blistering disorders including Dermatitis herpetiformis (DH), associated with a gluten-sensitive enteropathy (GSE), Bullous pemphigoid (BP) characterized by the presence of IgG autoantibodies specific for certain hemidesmosomal BP antigens, pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus.

Cryopyrin-associated periodic syndrome (CAPS) is a spectrum of disorders associated with mutations in NLRP3, including familial cold autoinflammatory syndrome, the Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.

Autoimmune Disorders of the Lung is a group including idiopathic nonspecific interstitial pneumonia (NSIP), asthma, Idiopathic Bronchiolitis Obliterans, Idiopathic Pulmonary Fibrosis, Idiopathic pulmonary alveolar proteinosis (I-PAP), and Goodpasture Syndrome. Collagen Vascular Diseases of the Lung are thought to often have an autoimmune component.

Idiopathic Inflammatory Myopathies (IIM) constitutes a heterogeneous group of diseases includes Primary idiopathic polymyositis, Primary idiopathic dermatomyositis, Polymyositis or dermatomyositis with malignancy, Juvenile dermatomyositis (or polymyositis), Polymyositis or dermatomyositis associated with other connective tissue diseases, Inclusion body myositis (IBM), Granulomatous Myositis,) Eosinophilic myositis, Focal Myositis and Orbital myositis.

Autoimmune neuritis is any inflammation of the nerves arising from the body's own immune system, and includes Guillain-Barre Syndrome and Miller Fisher Syndrome. GBS is often preceded by a viral or bacterial infection, surgery, immunization, lymphoma, or exposure to toxins. Demyelination occurs in peripheral nerves and nerve roots, and weakness of respiratory muscles and autonomic dysfunction may occur. Miller Fisher Syndrome involves oculomotor dysfunction, ataxia, and loss of deep tendon. The ataxia is produced by peripheral sensory nerve dysfunction. Facial weakness and sensory loss may also occur. The process is mediated by autoantibodies directed against a component of myelin found in peripheral nerves.

IBD is a generic term for an entire family of disorders, the most important of which are Ulcerative colitis and Crohn's disease, but also includes lymphocytic colitis, collagenous colitis, Ischaemic Colitis, Behçet's Syndrome, and Infective Colitis. IBD arises from a

ranges of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, for example are idiopathic.

The Autoimmune hepatobiliary diseases (AIHBD) comprise autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and the overlap syndromes.

Polyglandular autoimmune (PGA) syndromes occur as Type I (also called Whitaker syndrome), Type II (which is autoimmune Addison's disease in combination with thyroid autoimmune diseases and/or type 1 diabetes mellitus) and Type III (which exists as PAS IIIA - Autoimmune thyroiditis with type 1 diabetes mellitus; PAS IIIB - Autoimmune thyroiditis with Pernicious Anemia, and PAS IIIC - Autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ-specific autoimmune disease, notably Celiac's, hypogonadism, and Myasthenia gravis)).

One broad category is the antibody mediated diseases, which includes (in addition to certain forms of the lupus family and some other disorders discussed above) Castleman's disease, Antibody-mediated autoimmune myocarditis, autoimmune hemolytic anemia (AIHA), myasthenia gravis, Lambert-Eaton myasthenic syndrome (LEMS), multifocal motor neuropathy, Graves' disease, Idiopathic thrombocytopenic purpura, Primary Sjögren's syndrome, stiff person syndrome, Relapsing polychondritis, Pure white cell aplasia, Epidermolysis bullosa acquisita, cramp-fasciculation syndrome and Isaacs syndrome (acquired neuromyotonia), although in some cases, these are mixed with other responses. These vary greatly in the nature of the self-antigen.

Other known autoimmune disorders, or disorders generally considered to be autoimmune also include Scleroderma, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), Meniere's disease, Omenn syndrome, Idiopathic

neutropenia, Premature ovarian failure, Idiopathic hypoparathyroidism, multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, and Addison's disease. There is also Silent thyroiditis, atrophic gastritis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic anemia, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, Stevens-Johnson syndrome, Alopecia areata, idiopathic sprue, lichen planus, Graves ophthalmopathy, sarcoidosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, Reiter's syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Retroperitoneal Fibrosis, Juvenile rheumatoid arthritis (JRA), Celiac disease, Vitiligo, "immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome" (IPEX), Autoimmune Atherosclerosis, autoimmune autonomic ganglionopathy, and many, many more.

B. Claim 19 is drawn to allergic diseases. The term "allergies", "allergic diseases" and the like are fairly broad, and are used is somewhat different ways by different people, and as a result, it is not always clear what the term denotes. There are four major categories that are normally included:

A. Atopic IgE mediated, e.g. eczema, allergic rhinitis and most forms of asthma

B. Non-atopic IgE mediated, including reactions to insect and spider bites, and reactions to certain drugs

C. IgG mediated, e.g. allergies to casein and other milk proteins, and gluten. (Type III Hypersensitivity)

D. T-cell mediated allergies, including poison ivy, nickel contact dermatitis, other forms of Allergic contact dermatitis. (Type IV Hypersensitivity, also called cell-mediated or delayed-type hypersensitivity, DTH).

Other types of reactions may or may not be considered as allergies. Thus, type II hypersensitivity is a cytotoxic reaction which involves IgM or IgG or both, including e.g. ABO incompatibility reaction, Rhesus disease may or may not be considered an allergy reaction. It is unclear whether aspirin sensitivity is an allergy or an intolerance. Whether there is such a thing as fluoride allergy is contested. Some consider all reaction to ordinary food additives as intolerance, but others believe that some of these are in fact allergic reactions.

C. "Modulating" would also include the opposite effect, where the cellular and/or humoral immune system is stimulated to cope with immunoinsufficiency arising from irradiation, chemotherapy, HIV, genetic disorders, age-associated damage etc. There are a significant number of Immunodeficiency Disorders, in two very different categories. Primary Immunodeficiency disorders are caused by inherited functional defects in the cells of the immune system, particularly B and/or T Lymphocytes. Examples include X-linked Agammaglobulinemia (Bruton's disease), Common Variable Immunodeficiency , Selective IgA Deficiency, DiGeorge Syndrome , Severe Combined Immunodeficiency Disease (SCID, which is actually heterogeneous group of conditions all associated with genetic defects in those lymphoid stem cells that are precursors for both T and B Lymphocytes. This causes functional impairment of both humoral and cell-mediated immunity), Wiskott-Aldrich

syndrome, Ataxia-Telangiectasia , and other inherited defects in the complement system, and defects in granulocyte function. Secondary immunodeficiencies are acquired defects in immune function resulting from a wide variety of soruces. These include drugs (e.g. cancer chemotherapeutic agents, Cyclosporin, and corticosteroids), infections of immune system cells (most notably HIV), disseminated cancers (malignancies that invade the bone marrow may crowd out immune system cells and their precursors), malnutrition, radiation therapy (bone marrow suppression, lymphocyte toxicity), Splenectomy (increased susceptibility to infection by encapsulated microorganisms), severe burns (loss of immunoglobulins through damaged skin) and chronic renal disease.

D. In addition, claim 19 includes preventing allergic disease, i.e. preventing a person from getting asthma, celiac disease (gluten allergy) etc. in the first place.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See ***In re Fisher***, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided at page 39-41 and page 193 does not give any daily dosage. Further, it is completely generic. That is, it is the same dosage for all disorders listed in the specification, which is a very substantial range of disorders.

(4) State of the Prior Art: The compounds are 8-hydroxy adenines with a particular substitution patterns in the 2-position and 9-position. So far as the examiner is aware, no

8-hydroxy adenines of any kind at all are presently in use for the treatment of any immune-oriented disorder.

(5) Working Examples: There are no working examples to the treatment of any actual disorder. Indeed, no biological data of any kind is presented.

(6) Skill of those in the art: This very much depends on the particular art area.

I. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and

causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE.

Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

II. Autoimmune disorders are among the most complex and difficult to understand of all major categories of human disease. An example of this is scleroderma, which kills thousands of Americans every year. It is not even clear if the disorder is best understood as a vascular disease, a fibrotic disease, or an immune disease. Its cause—or causes—remains murky. Its molecular mechanisms or genetic origins have never been nailed down. Partially as a result, no compound has ever been established as effective in treating the disorder itself. While anti- TGF- β drugs have been given to reduce fibrotic scars, and ACE inhibitors provided to protect the kidneys, and still others are given to combat pulmonary hypertension, none of these combat scleroderma itself. While some general immunosuppressive drugs showed promising results even in Phase II studies, as of the filing date, and even now, none have ever been established as effective against scleroderma. GBS and Miller Fisher Syndrome are both quite refractory. Conventional immune suppressant drugs such as methylprednisolone have not been effective, and so the skill level in these disorders is low. Only plasma exchange therapy and intravenous immune serum globulin (IVIG) have proven effective. CAPS can be treated only with monoclonal antibodies against interleukin 1 or interleukin 1ß, a modality useless against most autoimmune disorders, which don't involve IL1. Examples of pharmaceutically untreatable autoimmune disorders include celiac disease, APECED, scleroderma and ALS. Medicines can be given to relieve symptoms, e.g. replace missing hormones, combat pulmonary hypertension or ameliorate pain, but these pharmaceuticals do not treat the disease itself. No study has firmly established any reliable treatment for Inclusion body Myositis.

Basically, there are two immune system, cell and humoral, and the claims cover both increasing and decreasing both of them, i.e. four different effects. Further, there are many different regulators involved in allergic reactions, including two different types of T-cells, IgE, IgM, IgG, B cells and others. Such a scope cannot possibly be deemed enabled. Further, claim 19 calls for something like prevention of allergic diseases. Asthma and celiac disease are for example, not considered preventable disorders. The skill level in preventing such disorders is essentially nil.

(7) The quantity of experimentation needed: Especially in view of points 1, 4, 5 and 6, the amount is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. ***In re Wright***, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Specification

In the abstract, spelling should be corrected of "siseases".

Claim Objections

A. A period appears after "respectively" in claim 2 (ninth from last line of page 5). A period appears at the end of the R4 definition in claim 1.

B. Claim 21 is improperly dependent on claim 1. Claim 1 does not provide for such compounds in the first place.

C. Claims 12-14 are objected to as duplicating claim 11. Whether the composition is called a composition, agent, medicament, etc., it is still the same physical object.

D. Claim 22, page 11, 8th from last species is missing a dash before the 9.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner, Art Unit 1624

7/6/2009